ABSTRACT

A DNA fragment distinct from the epidermal growth factor receptor (EGFR) and *erb*B-2 genes was detected by reduced stringency hybridization of *v-erb*B to normal genomic human DNA. Characterization of the cloned DNA fragment mapped the region of *v-erb*B homology to three exons with closest homology of 64% and 67% to a contiguous region within the tyrosine kinase domains of the EGFR and *erb*B-2 proteins, respectively. cDNA cloning revealed a predicted 148 kd transmembrane polypeptide with structural features identifying it as a member of the *erb*B family, prompting designation of the new gene as *erb*B-3. It was mapped to human chromosome 12q11−13 and was shown to be expressed as a 6.2 kb transcript in a variety of normal tissues of epithelial origin. Markedly elevated *erb*B-3 mRNA levels were demonstrated in certain human mammary tumor cell lines. These findings indicate that increased *erb*B-3 expression, as in the case of EGFR and *erb*B-2, plays a role in some human malignancies. Using *erb*B-3 specific antibodies (polyclonal or monoclonal), the *erb*B-3 protein was identified as a 180 kDa glycoprotein, $gp180^{erbB-3}$. The intrinsic catalytic function of $gp180^{erbB-3}$ was uncovered by its ability to autophosphorylate *in vitro*. Ligand-dependent signaling of its cytoplasmic domain was established employing transfectants which express a chimeric EGFR/*erb*B-3 protein, $gp180^{EGFR/erbB-3}$. EGF induced tyrosine phosphorylation of the chimera and promoted soft agar colony formation of such transfectants. These findings, combined with the detection of constitutive tyrosine phosphorylation of $gp180^{erbB-3}$ in 4 out of 12 human mammary tumor cell lines, implicate the activated erbB-3 product in the pathogenesis of some human malignancies. Thus, this invention also relates to a method for detecting a receptor ligand capable of either activating or down-regulating the receptor protein, as well as procedures for purifying the resultant ligand; a method of screening potential ligand analogs for their ability to activate the receptor protein; and procedures for targeting a therapeutic drug to cells having a high level of the receptor protein.